Phenotypes of Arrhythmogenic Cardiomyopathy

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Arrhythmogenic Cardiomyopathy (ACM) is a Mendelian disorder that can affect both left and right ventricles. It is most often associated with pathogenic desmosomal variants that can lead to fibrofatty replacement of the myocardium, a pathological hallmark of this disease.

arrhythmogenic cardiomyopathy | fibrofatty infiltration | cardiomyopathies

1. Introduction

Myopathies encompass both inherited and acquired disorders of the muscular system, including congenital myopathies (i.e., present at birth), muscular dystrophies (i.e., progressive skeletal myopathies), endocrine myopathies (e.g., Cushing's Syndrome), cardiomyopathies (e.g., dilated and hypertrophic), and more recently, the COVID-19 pandemic has resurfaced myocarditis (i.e., infectious myopathies). Arrhythmogenic cardiomyopathy (ACM) is an inherited heart disease that can affect both left and right ventricles, or even both, and is plagued by progressive muscle deterioration, fatal arrhythmias, exercise-induced disease penetrance, and cardiac fibrosis. Although ACM is not an infectious cardiomyopathy, it presents with distinct inflammatory pathologies observed in viral and/or bacterial myocarditis.

2. Phenotypes of Arrhythmogenic Cardiomyopathy

Arrhythmogenic Cardiomyopathy, commonly referred to as Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), is a myocardial disorder that can affect the right (ARVC), the left (ARLV), or both ventricles; hence its recent and more inclusive nomenclature—ACM. Pathologically, the two most uniquely specific traits of ACM are cardiac inflammation and fibrofatty replacement of the myocardium [1]. This progressive myocardial replacement is linked with ICD protein disarrangement that is associated with pathogenic desmosomal variants [2]. These gene variants lead to dysfunctional proteins responsible for structural and electrical connections between cardiomyocytes, leading to cardiomyocyte apoptosis/necrosis. Cardiomyocyte loss is considered one of the triggers leading to myocardial inflammation [3][4], where inflammation precedes fibro-fatty replacement of the myocardium.

The diagnosis of ACM can be elaborate considering symptoms can go undetected for years [5][6]. ACM patients harboring a known pathogenic gene variant may not present with any phenotypes (i.e., asymptomatic gene carrier), even though this identical gene and specific variant may be present in an aged-match symptomatic ACM patient. Hence, ACM is often described as reduced penetrance with variable expressivity. Sadly, and too often, the first

presentation is sudden cardiac death/arrest (SCD/A). That said, common features include exertional syncope, cardiac dysfunction (reduced percent ejection fraction [%EF] <40%), >500 ventricular extrasystoles in 24 h, T-wave inversions in precordial leads V1-V6, epsilon waves, ventricular arrhythmias of left bundle branch block (LBBB) pattern, and ventricular tachycardia (VT) [6][7]. Mechanical and electrical dysfunction is more frequently seen in the RV free wall (RVFW) and outflow tract (RVOT), hence ARVC is more commonly used in the field. However, ALVC and biventricular (i.e., ACM) forms have been identified [8]. Magnetic resonance imaging (MRI) can also support diagnosis with findings such as ventricular wall thinning, dyskinesia and hypokinesia, reduced %EF and percent fractional area change (%FAC), and myocardial fibrosis/scar using late gadolinium enhancement-MRI (LGE-MRI) or in some instances, an endomyocardial biopsy [9]. Some cases are difficult to diagnose via MRI and/or echocardiography, thus computed tomography angiography may be recommended. This diagnostic technique can reveal the presence of ventricular wall swelling (i.e., aneurysms) and akinetic regions—once called the “triangle of dysplasia” [10][11]. Considering that fibrofatty tissue can cause electrical conduction block (i.e., re-entrant VT) or persistent arrhythmias even with antiarrhythmics, an electrophysiological study may be necessary to find the site of electrical storms for VT-ablation [12]. Regardless of index presentation, LV dysfunction is a common phenotype at the time of transplantation; where the most frequent attestation for transplant is heart failure (HF) [13]. Although HF was originally considered to be rare in ACM [14], recent studies by Gilotra NA et al. demonstrated that at least one symptom of HF was present in 49% (n = 142/289) of ACM patients [15].

Since there are diagnostic complications, such as patients diagnosed with myocarditis at index presentation, genetic screening can reveal the presence of specific pathogenic variants that are associated with ACM [16]. Considered a “disease of the cardiac desmosome”, as >60% of cases involve pathogenic variants in desmosomal genes, ACM is a familial heart disease with the majority of cases involving autosomal dominant inheritance [9]. Although rare, autosomal recessive inheritance, compound heterozygosity and/or digenic mutations have been documented [9]. The most prevalent mutated protein is in the encoding gene *plakophilin-2* (*PKP2*), critical for intracellular adhesion to the cytoskeleton [17]. Additionally, mutations in desmosomal genes *desmoglein-2* (*DSG2*), *desmocollin-2* (*DSC2*), *desmoplakin* (*DSP*), and junctional *plakoglobin* (*JUP*) are associated with loss of adhesion and altered Ca^{2+} signaling [18][19][20]. Recently identified, mutations in the gene *CDH2*, which encodes a cadherin-2 protein, a major component of the adherent junction system [21], and the ion channel gene *sodium voltage-gated channel alpha subunit-5* (*SCN5A*) are reported to cause ACM through non-canonical pathways [22]. *Desmin* (*DES*) mutations have also been associated with ACM [23]. Correlation analyses of the genetic variants connected to ACM were published by Hoorntje et al., identifying prevalence and inheritance within each mutation [20].

In addition to the cardiac phenotypes ACM patients develop, there are, sadly, QOL changes ACM patients will encounter and for some, must implement in everyday life. For example, patients who recently had a VT storm, or an ICD discharge are restricted from driving. Although driving restrictions are dependent upon the state in which the patient resides, driving restrictions can range from 3–12 months. Even a simple day at the beach or lounging at the pool can be a life-altering event. Syncope, VT storm, or an ICD shock may limit a patient’s independence, as a “buddy system” is essential—even at a depth of 2 inches of water—for fear of drowning. Furthermore, ACM patients often confront the burdens of psychological stress, such as ICD implantation, ICD shocks (e.g.,

appropriate, or inappropriate discharges), and starting a family—as trepidation of passing down a pathogenic variant is possible. Although not all of these QOL changes are applicable to all heart diseases, ACM presents with considerable phenotypic overlap with the other two cardiomyopathies: hypertrophic (HCM) and dilated cardiomyopathy (DCM).

Dilated Cardiomyopathy is a disease of the cardiac muscle which causes decreased myocardial performance, systolic dysfunction, and ventricular dilation, that may or may not present with hypertension, and can manifest as an ischemic or non-ischemic disease [24][25][26]. Ischemic DCM manifests via extensive myocardial apoptosis/necrosis [27][28] typically following an acute myocardial infarction, while non-ischemic DCM shows no abnormal loading conditions [29] and represents the majority of clinical cases. Around 35% of DCM cases are familial inherited, while the other 65% are acquired throughout the patient's life. Acquired DCM can arise from environmental infections, autoimmune diseases, endocrine diseases, muscular dystrophy, and/or long-term alcohol abuse [30][31]. DCM symptoms vary and can present as fatigue, weight gain, thromboembolism, and chest pain [32] [33]. Although DCM patients present a lower burden of comorbidities, HF—more specifically HF with reduced ejection fraction—is the most common cause of mortality in DCM patients [29]. By the identification of DCM's features, monitoring and treatment are recommended for patients. Monitoring by electrocardiography (ECG) reports can be somewhat limited, and a variety of ECG morphologies and features are found for both genetic and/or acquired forms of DCM [34]. Some of these findings are LV hypertrophy (LVH) as observed by increased QRS amplitude and duration, left atrial (LA) enlargement seen via a biphasic ("notching") P-wave, LBBB, atrial fibrillation, repolarization abnormalities, and inferior T-wave inversions [31][35]. Electrical conduction abnormalities are particularly prevalent in inherited DCM, and are likely to present as sinus node dysfunction, sinus node arrest, intraventricular conduction delay, depolarization abnormalities, and supra- and ventricular arrhythmias [36]. Of particular note, the presence of intraventricular conduction dyssynchrony can result in decreased ventricular systolic function and mitral regurgitation, an indication of HF [37][38]. An additional clinical presentation of DCM is elevated levels of troponin-T (TNNT), a serum biomarker indicative of cardiomyocyte degeneration [39]. Myocardial infarction can also be identified through LGE-MRI, which can assess the levels of ischemic myocardium [40]. In inherited DCM, genetic mutations underlying this disease are commonly associated with components of the cytoskeleton and sarcomere [41]. The most common genes encoding sarcomeric proteins that are affected in DCM are: *β-myosin heavy chain* (*MYH7*) [42], *TNNT2* [43], *α-tropomyosin* (*TPM1*) [44], *troponin-C1* (*TNNC1*) [45], *TNNI3* [46], *titin* (*TTN*) [47], and *actin* (*ACTC1*) [48]. Mutations in the structural and functional gene *DES*, a component of the intermediate filament, cause DCM and can be concomitant—or not—with skeletal myopathies [49] [50]. Another genetic mutation known to contribute to features of DCM is the nuclear envelope protein *lamin-A/C* (*LMNA/C)* [51], which is also associated with Emery–Dreifuss muscular dystrophy and ACM [52][53][54]. On an important note, different myosin heavy chain isoforms can be found in DCM. The β- and α- isoforms are selectively associated with phenotypic modifications and disease progression to HF [55]. Although a variety of genetic mutations are associated with DCM, the most common findings are reduced Ca^{2+} affinity and contractility [56][57].

Hypertrophic Cardiomyopathy is primarily considered an inherited cardiac disorder and presents distinct characterizations, such as thickening (i.e., hypertrophy) of the LV free wall and septum [58]. The development of LVH is not associated with any other evident cause, such as systemic or metabolic diseases [59], and thus HCM is

considered a primary heart disease. Symptoms of HCM vary depending on the severity of the condition and age and include shortness of breath, chest pain, palpitations, fatigue, pulmonary congestion, and swelling of the legs (i.e., peripheral edema) [60][61]. The development of HF in HCM is a major concern due to obstruction of blood flow [62]. Diagnosis of HCM rarely occurs via ECG, as most cases show a normal ECG, yet some distinct features include the presence of LVH (e.g., increased QRS amplitude and “QRS widening”) and left-axis deviation. Predominantly, an HCM diagnosis is acquired through transthoracic echocardiography with Doppler, to assess the presence of LV outflow tract obstruction, mitral valve regurgitation, and diastolic dysfunction [63][64][65]. Utilization of MRI or angiogram can offer additional information if phenotypic features are difficult to determine and/or are inconclusive. Utilization of an MRI more adequately evaluates LV wall parameters (e.g., posterior, and anterior wall thickness), %EF, basal asymmetrical septal hypertrophy, apical HCM, and systolic, diastolic, and mitral valvular dysfunction. Lastly, LGE-MRI is a useful tool in the assessment of myocardial scar [64][65][66][67]. In the majority of HCM cases, the disease is autosomal dominant, although less common autosomal recessive and X-linked inheritance have been identified [68]. The first identified and most common gene mutation associated with HCM is *MYH7* [69][70]. Other gene-encoding proteins that are liable for HCM are *myosin binding protein-C* (*MYBPC3*) [71][72], and other sarcomeric proteins [73], which are also associated with DCM, such as *TNNT2* [74][75][76][77], *TNNI3* [78], *TNNC1* [79][80], *TPM1* [81], and *ACTC* [82]. Together, *MYH7* and *MYBPC3* genes account for nearly 50% of cases [68]. Similarly, to DCM, the majority of the HCM mutations are sarcomeric components or are associated with the contractile apparatus, making HCM and DCM distinguishable by their unique dysfunctional myocardial contractility [83]. Although troponin mutations have been associated with increased myofilament Ca^{2+} sensitivity [79], genetic penetrance also dictates phenotype severity (i.e., *TPM1* causes mild HCM) [84].

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